Mental distress and personality in women undergoing GnRH agonist versus GnRH antagonist protocols for assisted reproductive technology

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**STUDY QUESTION:** Do mental distress and mood fluctuations in women undergoing GnRH agonist and GnRH antagonist protocols for assisted reproductive technology (ART) differ depending on protocol and the personality trait, neuroticism?

**SUMMARY ANSWER:** ART treatment did not induce elevated levels of mental distress in either GnRH antagonist or agonist protocols but neuroticism was positively associated with increased mental distress, independent of protocols.

**WHAT IS KNOWN ALREADY:** ART treatment may increase mental distress by mechanisms linked to sex hormone fluctuations. General psychological characteristics, such as personality traits indexing negative emotionality, e.g. neuroticism, are likely to affect mental distress during ART treatment.

**STUDY DESIGN, SIZE, DURATION:** A total of 83 women undergoing their first ART cycle were consecutively randomized 1:1 to GnRH antagonist (n = 42) or GnRH agonist (n = 41) protocol. The study population was a subgroup of a larger ongoing Danish clinical randomized trial and was established as an add-on in the period 2010–2012.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Women in the GnRH antagonist protocol received daily injections with recombinant follicle-stimulating hormone, Puregon® and subcutaneous injections with GnRH antagonist, Orgalutran®. Women in the GnRH agonist protocol received nasal administration of the GnRH agonist, Synarel® and subcutaneous injections with FSH, Puregon®. The study design did not allow for a blinding procedure. All women self-reported the Profile of Mood States, the Perceived Stress Scale, the Symptom Checklist-92-Revised, and the Major Depression Inventory questionnaires, at baseline, at ART cycle day 35, on the day of oocyte pick-up, and on the day of hCG testing. Also, a series of Profile of Mood States were reported daily during pharmacological treatment to monitor mood fluctuations. The personality trait Neuroticism was assessed at baseline by the self-reported NEO-PI-R questionnaire.

**MAIN RESULTS AND THE ROLE OF CHANCE:** ART did not induce within- or between-protocol changes in any of the applied measures of mental distress. However, the GnRH antagonist protocol was associated with more pronounced median mood fluctuations during the stimulation phase (agonist, 11.0 SD, [IQR = 21.1–6.1]; antagonist, 8.9 SD, [IQR = 11.3–5.7], P = 0.025). This association became non-significant after applying a Bonferroni–Holm correction. Neuroticism was highly positively associated with increased levels of mental distress throughout treatment independent of protocols (all P-values <0.006), and cross-sectional analysis revealed that women with high or low Neuroticism scores at baseline showed a significant trend towards lower chances of a positive pregnancy test (P-value = 0.028).

**LIMITATIONS, REASONS FOR CAUTION:** Information on prognostic factors such as preceding length of infertility, number of retrieved oocytes and number of prior insemination treatments was not accounted for in the analyses. The stratification of protocols by age in the subgroups of women included in this study was suboptimal. Women with prior or current use of antidepressant medication were excluded from our study.

**WIDER IMPLICATIONS:** Our results imply that mental distress emerging during ART treatment is not causally linked to hypogonadism per se but is associated with neuroticism.
or to the choice of protocol. Rather, our data highlight the potential importance of (i) rapid increases in ovarian steroids and (ii) addressing personality traits indexing negative emotionality, i.e. Neuroticism, in women undergoing ART treatment, to optimize both emotional adjustment and, possibly, the chances of obtaining pregnancy.

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**Key words:** mental distress / personality / assisted reproductive technology / ovarian stimulation protocol / neuroticism

## Introduction

Women and men with fertility problems often experience their situation as highly stressful (Cousineau and Domar, 2007). The strain of undergoing assisted reproductive technologies (ART) is also well-documented (Hammarberg et al., 2001; Verhaak et al., 2007), reflected by the fact that psychological burden is a major reason for discontinuing treatment (Olivius et al., 2004; Gameiro et al., 2012). Such adverse psychological effects of ART treatment could have a negative impact on both mother and infant future health (O’hara and Swain, 1996; Eugster and Vingerhoets, 1999; Brouwers et al., 2001; Hjelmstedt et al., 2003; Alder et al., 2007), and currently it is not clear if mental distress experienced by women undergoing ART treatment is associated with chances of obtaining pregnancy (Boivin et al., 2011; Matthiesen et al., 2011). ART treatment may increase mental distress in women through a complex set of biological and psychological factors; controlled ovarian stimulation in ART is achieved by the pharmacological induction of sex steroid hormone changes, which could influence levels of mental distress as sex steroid hormones may play a role in the regulation of mood and the pathophysiology of mood disorders (Payne, 2003; Douma et al., 2005; Freeman et al., 2006, 2014; Munk-Olsen et al., 2006; Deecher et al., 2008).

Especially, the administration of gonadotrophin-releasing hormone (GnRH) agonists has been coupled to negative mood symptoms, typically attributed to medically induced hypogonadism (Warnock et al., 1998; Patten and Barbui, 2004). Interestingly, adverse responses to changes in sex hormone levels appear only to affect a subgroup of women undergoing ART treatment (Van den Broeck et al., 2010; Bloch et al., 2011). Therefore identifying individual markers of susceptibility is pivotal to enable targeted prevention. The psychological construct of Neuroticism indexes individual differences in the tendency to experience negative emotions, impulsiveness, anxiety and angry hostility, and vulnerability to stress (McCrae and Costa, 2003). High Neuroticism scores have been associated with risk for major depression (Kendler and Myers, 2010), also in the context of stress (Jacobs et al., 2006), psychopathology in general (Ormel et al., 2013), and increased release of the stress hormone cortisol (Portella et al., 2005; Nater et al., 2010). However, the role of Neuroticism for ART-induced mental distress is at present unknown. In this study, we tested the following hypotheses: (i) women in the GnRH agonist protocol exhibit increased levels of mental distress compared with women in the GnRH antagonist protocol; (ii) mood fluctuations are more pronounced in the GnRH agonist protocol compared with the GnRH antagonist protocol; and (iii) neuroticism interacts with the protocols and independently affects levels of mental distress and mood fluctuations.

## Method

### Participants

A total of 83 eligible women (mean age: 33.1 ± 4.8, range: 22–39 years) undergoing their first ART cycle were consecutively randomized 1:1 to a GnRH antagonist (n = 42) or GnRH agonist (n = 41) protocol by a project nurse, stratified by age (≤ 36 years and > 36 years) and the need for (ICSI or general) IVF. The study population was a subgroup of a larger ongoing Danish clinical randomized trial evaluating treatment outcome of the two protocols and was established as an add-on to the overall study in the period 2010–2012. Exclusion criteria were: prior IVF treatment, uterine anomalies, testicular sperm aspiration (TESA) needed, allergy to the ingredients used in the pharmacological treatment, reduced kidney or liver function, women >40 years of age, or prior or current use of antidepressant medication. The study was registered as a clinical trial (EudraCT – 2008-005452-24) and approved by the Ethics Committee for the Capital Region of Denmark (H-B-2008-109). All participants signed an informed consent form.

### Intervention

Women in the GnRH antagonist protocol received daily injections with the recombinant follicle-stimulating hormone (FSH) analogue, Puregon®, to initiate ovarian stimulation (150, i.e. ≤ 36 years, and 225, i.e. >36 years, respectively) starting at cycle day 2–3. After 5 days of stimulation treatment, the women received additional daily subcutaneous injections with the GnRH agonist, Orgalutran® (1 × 0.25 mg). Women in the GnRH agonist protocol received daily nasal administration of the GnRH agonist, Syranel®, to suppress ovarian hormone production (200 mg × 3 daily) starting at cycle day 21. After 14 days of GnRH agonist administration (cycle day 35), the women received additional daily injections with Puregon® (150, i.e. ≤ 36 years and 225, i.e. >36 years, respectively). Nasal administration of Syranel® was continued (200 mg × 2 daily) until the day of oocyte pick-up. In both protocols, ovulation induction was induced by subcutaneous injection with Ovitrelle® (6500, i.e.), when the three largest ovarian follicles had a diameter ≥ 17 mm. Oocyte retrieval was performed 36–38 h later.

### Measures

#### Time points for data collection

Figure 1 is an overview of the study design. Participating women completed their questionnaires using a secure online survey system (https://survey.nru.dk/). Baseline questionnaires (T0) were completed at home on the day of inclusion and randomization. A computer was set up at the fertility clinic, which the women accessed to complete their questionnaires when routinely attending the clinic for treatment at three time points: when ovarian stimulation was initiated (T1) [at cycle day 35 for women in the agonist protocol]; on the day of oocyte pick-up (T2); and on the day of hCG-testing (T3). In addition, mood was reported daily during the pharmacological treatment from...
The Profile of Mood States (POMS) is used to assess transient, distinct mood states. The POMS comprises 65 adjectives (e.g., ‘Furious’, ‘Hopeless’ and ‘Carefree’) on a 5-point Likert scale from 1 (not at all) to 5 (extremely) based on the recollection of ‘the last 24 h’ for six factors and a total score of mood disturbance rated by 65 adjectives described above as attendance points for questionnaires (T1, T2 and T3).

The Neuroticism domain comprises 48 items (e.g. ‘I am not a worrier’ or ‘I often get angry at the way people treat me’) rated on a 5-point Likert scale from 0 (strongly disagree) to 4 (strongly agree). Individuals who score high on Neuroticism tend to experience difficulties in coping with stress and interpret the world around them as threatening and frustrating, which make them more prone to experience anxiety, anger, guilt, stress or sadness. In the present sample, internal consistency (Cronbach’s alpha, $\alpha$) for the Neuroticism domain was high, $\alpha = 0.91$.

The Major Depression Inventory (MDI) is a rating scale of depressive symptoms according to DSM-IV and ICD-10 diagnostic criteria (Bech et al., 2001). It comprises 10 items (e.g. ‘Have you felt very restless?’ or ‘Have you suffered from reduced appetite?’) rated on a 6-point Likert scale from 0 (never) to 5 (all the time) based on the recollection of the last 2 weeks. The MDI was completed at T0, T1, T2 and T3. Internal consistency for the MDI was high, $\alpha = 0.88$.

Plasma estradiol
Venous blood was drawn from all women at T0, T1, T2 and T3. Plasma was kept at a temperature between 2 and 8°C until analysed on a routine basis at the hospital laboratory after a maximum of 7 days. Estradiol concentrations were determined by electrochemiluminescence immunoassays (ECLIA) on a Cobas E601 Immunology Analyzer (Roche, Mannheim, Germany) with a lower detection limit of 0.02 nmol/l.
Statistical analyses

Main analyses
Demographic data were analysed using Student’s t-tests or Mann–Whitney’s U-tests for continuous data and Chi-square tests ($\chi^2$) for categorical data. Friedman’s test was used to examine ART-induced changes in mental distress and plasma estradiol within the protocols and Kruskal–Wallis one-way analysis of variance of the pair wise change (from T0 – T2) was used to examine differences in ART-induced changes in mental distress between the protocols. For interaction analyses, we used a general linear model adjusted for baseline measures of mental distress, age and BMI. Likewise, we used a general linear model for our cross-sectional analyses of Neuroticism effects on mental distress adjusted for age and BMI. Mann–Whitney’s U-test was used to compare protocol differences in mood fluctuations. Levels of mood disturbances over the course of treatment fluctuated around a quite stationary mean in both protocols. This was evaluated using generalized estimating equations with independence working correlation.

Friedman’s test was used to examine ART-induced changes in mental distress from baseline (T0) to the day of oocyte pick-up (T2), including the suppression phase for women in GnRH agonist protocol (T1) (Table II). Furthermore, we observed no differences in changes of mental distress from baseline (T0) to the day of oocyte pick-up (T2) between the agonist and antagonist protocols (all P-values > 0.125). We conducted a post hoc Friedman’s test, which further included the day of hCG-testing (T3) for the subgroup of women who had embryos transferred (Fig. 1). Here, a significant effect was observed for women in the GnRH antagonist protocol (Table II). Analyses of pair wise change (Kruskal–Wallis) showed a decrease in median perceived stress (PSS) from the day of oocyte pick-up (T2) to the day of hCG-testing (T3) for these women (T2, 13.0 PSS [IQR = 18.0–7.0]; T3, 10.0 PSS [IQR = 16.0–5.8], P = 0.036). Changes in estradiol during pharmacological treatment were assessed by calculating a change score ($\Delta$) for each woman ($T3 - T0$) for all women and ($T1 - T0$) for women in the agonist protocol only ($\Delta$agonist, 3.30 ± 2.57 nmol/l; $\Delta$gonist, 3.74 ± 2.57 and $-$0.11 ± 0.09 nmol/l, respectively). Neither the absolute concentrations of estradiol nor the magnitude of changes during pharmacological treatment were associated with levels of mental distress (all P-values > 0.203).

Follow-up analysis
We conducted a follow-up cross-sectional analysis to examine whether baseline Neuroticism predicted probability of positive pregnancy test (as defined by hCG > 50 ui/l). This was analysed using logistic regression allowing a non-linear function of Neuroticism and measures of mental distress modelled flexibly using a natural cubic spline with a single knot at the median of the predictor adjusted for age, protocol and BMI (Harrell, 2001). All analyses were performed in SPSS (version 20.0) and R (version 3.0.1) (Team, 2013). We used a significance level of $\leq$ 0.05 and all hypothesis-tests were considered two-sided.

Results

Baseline data
Descriptive data for women in the GnRH antagonist and GnRH agonist protocols are shown in Table I. Median age differed significantly between the two protocols (antagonist, 31.2 years [IQR = 35.5–28.4]; agonist, 36.4 years [IQR = 37.6–32.7], P = 0.001). No women presented with clinical levels of psychopathology at baseline, according to established Danish criteria for clinical cut off scores on the SCL-92-R (Olsen, Mortensen and Bech, 2006), and no significant protocol differences were observed on measures of mental distress (Table I). Plasma concentrations of estradiol were not associated with measures of mental distress or Neuroticism at baseline (all P-values > 0.251); however, Neuroticism scores were, as expected, positively associated with mental distress at baseline (all P-values < 0.001, two-tailed).

Changes in mental distress
Contrary to our hypotheses, we observed no significant ART-induced, within protocol changes in mental distress from baseline (T0) to the day of oocyte pick-up (T2), including the suppression phase for women in GnRH agonist protocol (T1) (Table II). Furthermore, we observed no differences in changes of mental distress from baseline (T0) to the day of oocyte pick-up (T2) between the agonist and antagonist protocols (all P-values > 0.125). We conducted a post hoc Friedman’s test, which

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Table I Descriptive baseline data.

<table>
<thead>
<tr>
<th>Descriptive variables</th>
<th>Antagonist</th>
<th>Agonist</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Age in years</td>
<td>31.2</td>
<td>36.4</td>
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<tr>
<td>[35.5–28.4]</td>
<td></td>
<td>[37.6–32.7]</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.9 ± 4.7</td>
<td>25.0 ± 5.6</td>
<td>0.817</td>
</tr>
<tr>
<td>Smoking (cigarettes per day)</td>
<td>0.5</td>
<td>0.6</td>
<td>0.705</td>
</tr>
<tr>
<td>Alcohol use (units per week)</td>
<td>1</td>
<td>1.2</td>
<td>0.433</td>
</tr>
<tr>
<td>Neuroticism scores</td>
<td>106.9 ± 22.0</td>
<td>84.7 ± 21.1</td>
<td>0.506</td>
</tr>
<tr>
<td>Mental distress</td>
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<td></td>
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</tr>
<tr>
<td>POMS</td>
<td>8.0</td>
<td>4.0</td>
<td>0.197</td>
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<td>[4.0–0.5]</td>
<td>[2.0–5.0]</td>
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<tr>
<td>PSS</td>
<td>13.5</td>
<td>11.0</td>
<td>0.298</td>
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<tr>
<td>[20.3–7.0]</td>
<td>[17.0–5.0]</td>
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<tr>
<td>MDI</td>
<td>6.0</td>
<td>6.0</td>
<td>0.407</td>
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<td>[16.3–3.8]</td>
<td>[9.0–4.0]</td>
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<td></td>
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<tr>
<td>SCL-92-R</td>
<td>0.3</td>
<td>0.3</td>
<td>0.529</td>
</tr>
<tr>
<td>[0.6–0.2]</td>
<td>[0.5–0.2]</td>
<td></td>
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</tr>
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</table>

Information obtained at baseline with medians and interquartile ranges in square brackets or means ± standard deviations and P-values of protocol differences. POMS, Profile of Mood States; PSS, Perceived Stress Scale; MDI, Major Depression Inventory; SCL-92-R, Symptom Checklist 92-Revised.
Neuroticism

Neuroticism significantly predicted mental distress throughout treatment (all \(P\)-values < 0.006), but did not interact with protocols (all \(P\)-values > 0.115). Higher Neuroticism scores at baseline were also significantly associated with more pronounced mood fluctuations during the stimulation phases across protocols (\(P = 0.035\)). In the cross-sectional follow-up analysis, a non-linear inverted U-shaped association was found, such that women with high or low Neuroticism scores at baseline showed a significant trend (\(P\)-value = 0.028) towards a lower probability of pregnancy (defined as hCG > 50 uI/l) (Fig. 2).

Discussion

We observed no significant changes in mental distress from baseline to the end of hormone stimulation, or a protocol × Neuroticism interaction, within or between the GnRH agonist and antagonist protocols. However, mood fluctuations were more pronounced during the stimulation phase for women in the GnRH antagonist protocol versus the GnRH agonist protocol. High Neuroticism scores were highly significantly associated with increased mental distress throughout treatment independent of protocols and with mood fluctuations during the stimulation phase. Also, a follow-up analysis suggested that women with high or low Neuroticism scores showed a significant trend towards a lower chance of pregnancy.

ART protocols and changes in mental distress

Contrary to our a priori hypothesis, the initial suppression phase in the GnRH agonist protocol was not associated with elevated symptoms of mental distress compared with baseline, suggesting that the initial suppression phase per se does not induce mental distress. Consistent with our findings, no exacerbations of mood symptoms during the hypo-gonadal phase were observed in women undergoing IVF treatment.
compared with baseline (Bloch et al., 2011). However, these findings contrast with an earlier study, where elevated symptoms of depression were observed during the hypogonadal phase in women undergoing their first cycle of conventional IVF treatment when compared with a mild ovarian stimulation with single embryo transfer protocol (de Klerk et al., 2006), and a smaller study, where symptoms of depression and anxiety progressively increased from baseline to the day of oocyte pick-up (Toren et al., 1996). The discrepant findings may to some extent reflect the use of different psychometric tools across studies. De Klerk et al. (2006) found elevated depressive symptoms during pituitary down-regulation using the self-reported Hospital Anxiety and Depression Scale (HADS) in women undergoing ART, unlike the present study and the study by Bloch et al. (2011), where no elevated levels of distress were found using SCL-92-R based measures. Toren et al. (1996) used the interview-based Hamilton Rating Scale and found elevated depressive symptoms during pituitary down-regulation corroborating de Klerk et al.’s (2006) findings. The HADS assesses only non-physical symptoms of anxiety and depression, while the SCL-92-R assesses a broad range of psychopathological symptoms and associated levels of global distress, making the latter more suitable for a global characterization of mental distress and the former more suitable for focusing on anxiety and depression in a medical population. Therefore it is possible that the SCL-92-R is less specific in detecting changes in mood and anxiety symptoms in women undergoing ART when compared with HADS. However, the women studied here presented with reproductive difficulties but were otherwise healthy and as de Klerk et al. (2006) did not exclude women with prior or current use of antidepressant medication, direct comparison between studies is difficult.

**Mood fluctuations during ART treatment**

Our data are consistent with the hypothesis that controlled ovarian hormone stimulation, in the absence of prior suppression of ovarian hormone production, is associated with more pronounced mood fluctuations. Rodent and non-human primate models suggest that both withdrawal from and exposure to ovarian hormones can potentially affect brain functions of relevance to emotional regulation and mood, such as serotoninergic signalling (Bethea et al., 2002; Lu et al., 2003; Suda et al., 2008). However, it is far from clear how rapid hormone fluctuations may affect mental distress and through which mechanisms or which phases of fluctuations are the more critical (Ben-Dor et al., 2013). Based on the current observations, we therefore speculate that prior treatment with GnRH agonists, at the time suppression is established, may dampen the potential adverse effects of subsequent controlled ovarian stimulation. However, correcting for multiple comparisons rendered the observation non-significant and replication is needed in order to validate this possible inter-protocol difference in mood fluctuations using a design with serial daily reports. The stimulation phase coincides with initiation of treatment in GnRH antagonist as opposed to GnRH agonist protocol. Therefore factors not induced pharmacologically (e.g. anxiety and expectation pressures related to the procedure) may also contribute to the observed differences in mood fluctuations.

**The role of neuroticism**

Neuroticism (i.e. negative emotions and stress vulnerability, impulsive and labile mood dispositions) was highly positively associated with increased levels of mental distress and with more pronounced mood fluctuations during the stimulation phase in both protocols. The latter suggests that higher levels of neuroticism combined with rapid increases in ovarian hormones may elicit adverse mood symptoms, such as unstable and labile mood. Corroborating this, similar personality constructs to Neuroticism have been coupled to subtle menstrual cycle disturbances (Demyttenaere et al., 1994), levels of ovarian reproductive hormones during the menstrual cycle (Ziomkiewicz et al., 2012), and infertility-related distress (Van den Broeck et al., 2010). High or low Neuroticism scores at baseline showed a significant trend towards subsequent negative pregnancy test. As Neuroticism is thought to be a risk marker for mental distress and depression, this is consistent with a meta-analysis on emotional distress and outcome of ART treatment in which perceived stress and trait/state anxiety showed a negative association with clinical pregnancy, and clinical depression showed a non-significant negative trend towards lower pregnancy rates (Matthiesen et al., 2011). Likewise, an adverse effect of Neuroticism and a positive effect of reducing stress on probability of pregnancy and live birth have been observed (Hämmerli et al., 2009; Volgsten et al., 2010). However, a recent meta-analysis did not report any association between pretreatment emotional distress and outcome of ART treatment (Boivin et al., 2011). The relatively few observations in the lower end of the Neuroticism spectrum in this study make interpretation of the association between low Neuroticism scores and chances of pregnancy somewhat inconclusive, as also reflected by the broad confidence interval (Fig. 2).
Distress and personality in ART-treated women

Of particular relevance for clinicians handling the treatment of subfertile women, personality appears to be a stronger predictor than choice of protocol for the mental distress experienced by women undergoing ART. If replicated, the ease of administration and the clinical relevance make ratings of Neuroticism an applicable tool for health care professionals in evaluating ART-related vulnerability to mental distress. Our tentative results also warrant further longitudinal investigation of the effect of personality and mental distress for successful ART treatment outcome, ideally with clinical end-points, such as number of live children born, and infant health measures.

Methodological considerations

The strength of this study is that it is part of a controlled randomized and prospective study with an extensive set-up of well-validated and reliable psychometric instruments covering the entire treatment cycle, including daily reports during pharmacological treatment. The study also took into account general psychological characteristics associated with increased risk of mood disorders, namely the personality trait, Neuroticism. However, the present findings should be interpreted under the following potentially important methodological limitations. First, even though only women undergoing their first ART-cycle were included, information on prognostic factors such as preceding length of infertility and number of prior inseminations was not accounted for in the analyses. Second, the stratification of protocols by age (≤36 years and >36 years) in this subgroup of women was not successful. Hence, women in the GnRH antagonist protocol were younger on average than those in the GnRH agonist protocol. Moreover, the different doses of Puregon® administered across protocols (150, i.e. ≤36 years and 225, i.e. >36 years, respectively) may have biased our results. However, age, group and BMI were included as covariates in our cross-sectional analyses. Third, women with prior or current use of antidepressant medication were excluded from our study. This is likely to have biased our study population towards low-risk women with lower Neuroticism scores. We may therefore have underestimated the effects of the stimulation phase on mood fluctuations and the predictive value of Neuroticism for mental distress and probability of pregnancy.

In conclusion, ART treatment did not induce elevated levels of mental distress and no differences between agonist and antagonist protocols or interactions with Neuroticism were observed. However, in the absence of prior ovarian hormone suppression (i.e. GnRH antagonist protocol), more pronounced mood fluctuations during the stimulation phase were observed, which was rendered non-significant after correcting for multiple comparisons. Neuroticism predicted levels of mental distress and the predictive value of Neuroticism for mental distress and probability of achieving pregnancy.

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Authors’ roles

D.S.S.: contributed to conception and design of the study and the acquisition of data; managed literature searches; organized and conducted the statistical analyses; wrote the first draft of the manuscript; contributed substantially to analyses and interpretation of the results; and revised the manuscript critically for important intellectual content. M.T.: contributed to conception and design of the study and the acquisition of data; carried out medical examinations of the participants; was involved in the statistical analyses; contributed substantially to analyses and interpretation of the results; and revised the manuscript critically for important intellectual content. L.V.H.: contributed to conception and design of the study; was involved in the statistical analyses; contributed substantially to analyses and interpretation of the results; and revised the manuscript critically for important intellectual content. K.K.H.: contributed considerably to analyses and interpretation of the results; conducted all modelling of the applied non-linear models; and revised the manuscript critically for important intellectual content. T.B.: carried out medical examinations of the participants; substantially contributed to analyses and interpretation of data; and revised the manuscript critically for important intellectual content. P.S.J.: conceived and designed the study; conducted all modelling of the applied non-linear models; and revised the manuscript critically for important intellectual content. V.G.F.: conceptualized and designed the study in collaboration with co-authors; participated in acquisition of data; managed literature searches; organized and contributed to the statistical analyses; contributed substantially to analyses and interpretation of the results; and revised the manuscript critically for important intellectual content. A.P.: carried out medical examinations of the participants; contributed considerably to analyses and interpretation of data; and revised the manuscript critically for important intellectual content. T.H.: recruited all participants; handled data collection; and revised the manuscript critically for important intellectual content. J.B.: carried out medical examinations of the participants; substantially contributed to analyses and interpretation of data; and revised the manuscript critically for important intellectual content. P.H.: carried out medical examinations of the participants; contributed considerably to analyses and interpretation of data; and revised the manuscript critically for important intellectual content.

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Conflict of interest

None declared.

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